Case Report

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Case Report: Sleep wake cycle disorder and agitation associated with Levetiracetam in an elderly patient with traumatic brain injury

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ABSTRACT

Rehabilitation following traumatic brain injury (TBI) in the elderly is challenging. They tend to have poorer functional outcomes and often have associated cognitive decline. Rehabilitation interventions directed towards functional recovery are often hampered by agitation, confusion and fatigue. Identifying and correcting all possible causes is imperative in aiding rehabilitation. We present a 76 year old man who was admitted to an intermediate neurorehabilitation unit for cognitive rehabilitation following TBI. He was on multiple antiepileptic drugs(AED) for post TBI seizures. He was noted to have persistent sleep wake cycle disorder and agitation which were attributed to his TBI and consequent cognitive decline .However following withdrawal of Levetiracetam from his AED drug regimen, there was a marked decrease in his agitation with gradual normalization of his sleep wake cycle. This in turn led to his better participation in the rehabilitation program.

KEYWORDS

Traumatic brain injury, Levetiracetam, Sleep wake cycle disorder, Agitation

Introduction:

In traumatic brain injury (TBI) the primary insult to the brain and the secondary insults as a result of systemic complications may result in a multitude of sequelae ranging from subtle neurological deficits to significant morbidity and mortality. As the brain recovers by repair and adaptation, changes become apparent and may result in physical, cognitive and psychosocial dysfunction. Rehabilitation is usually structured to recover physical ability, cognitive and social retraining with the aim of gaining independence in activities of daily living.

Case Report:

A 76 year old male patient was admitted to an intermediate neurorehabilitation unit following a traumatic brain injury(TBI) .He had fallen from a height of 11 feet resulting in intracerebral haemorrhage in the left parietal lobe and a left parietotemopral subarachnoid hemorrhage which was managed conservatively in the neurosurgical unit. He developed recurrent post traumatic seizures in the form of myoclonic jerks for which he was started on antiepileptic drugs (AEDs) sodium valproate ,clobazam and levetiracetam .During his stay in the acute neurorehabilitation unit, he was noted to be confused and wandering with a disrupted sleep wake cycle. Cognitive assessment showed global impairment across all cognitive domains suggesting that cognitive impairment was secondary to TBI with the chaotic sleeping pattern and fatigue having a significant effect on his cognition. He was then transferred to an intermediate neurorehabilitation unit four months post head injury for rehabilitation prior to discharge.

On admission he was confused, and disorientated. His neurological examination was normal except for mild expressive dysphasia. On the first night of his stay in the unit, he did not sleep at all, was restless, agitated and aggressive towards the staff. His initial agitation was attributed to the change of surroundings and general disorientation. However during his first week at the rehabilitation unit it was noted that his sleep wake cycle was completely disrupted .He would have short fragmented naps through the day and would regularly get agitated at night with threatening behaviour towards staff. On admission the Rancho Los Amigos scale[†] was 4(confused-agitated) and he needed specialized supervision. Despite environmental modification and optimal pharmacotherapy to improve sleep and decrease agitation, the patient still continued to have aggressive outbursts and no identifiable sleep wake pattern. It was noted by the nursing staff that occasionally when very agitated, the patient refused to have his night time medications including all AEDs .On such occasions he was reported to have slept better at night and did not have any daytime naps. All blood investigations were within normal limits except for mild hyponatremia with a normal creatinine clearance and CT head showed changes consistent with previous TBI with no new pathology .A neurology opinion was sought and with a Naranjo adverse drug reaction probability score[††] of 7/10, a decision was taken to slowly decrease levetiracetam and wean it to stop, while continuing all other regular AEDs. The levetiracetam was reduced from an original dose of 750mg twice daily by 500mg every week with an aim to stop. This resulted in a considerable improvement in the patient's agitation with a complete halt in the nighttime aggressiveness. His sleep wake cycle normalized and he started

sleeping longer at night. His Ranchos Los Amigos scale improved from 4(confused-agitated) to 6(confused-appropriate). The patient could now participate more with the team of trained therapists in memory and attention exercises as well as regaining independence in activities of daily living.

Discussion:

TBI particularly in elderly aged over 64 years has a worse functional outcome as compared to non elderly.[1]Closed head injury in older adults produces considerable cognitive deficits in the early stages of recovery[2] and there have been studies suggesting TBI to be a risk factor for developing Alzheimer's disease.[3]Memory deficits, attention problems, loss of executive function and confusion are common after TBI.[4]This impaired cognitive function reduces the patient's ability to recognize environmental stimuli often resulting in agitation and aggression towards perceived threats.TBI by itself may result in a variety of sleep disorders ranging from hypersomnia, narcolepsy, alteration of sleep wake cycle, insomnia to movement disorders[5]Sleep wake schedule disorders following TBI are relatively rare and may clinically present as insomnia.[6]Often these sleep disorders result in additional neurocognitive deficits and functional impairment, which might often be attributed to the original brain injury itself and thus be left without specific treatment.

While dealing with disrupted sleep pattern and agitation in the elderly following TBI, treatable causes such as neurological, infectious, metabolic, and medications should be ruled out. This is imperative as they disrupt rehabilitation and achievement of functional goals. Long duration of agitation post TBI has been associated with longer duration of rehabilitation stay and persisting limitations in functional independence.[7]After ruling out all the treatable causes the first focus is on environmental management with provision of a safe, quiet, familiar, structured environment while reducing stimulation and providing emotional support. The next step is introduction of pharmacotherapy to reduce agitation. Though a variety of pharmacological agents are available, there is no firm evidence of efficacy of any one class and often the choice of drug is decided by monitoring its effectiveness in practice and watching for side-effects.[8]In pharmacotherapy, the general principle followed is start low and go slow while developing clear goals to help decide when to wean and stop medications. Atypical antipsychotics are often used for the agitation while benzodiazepines and non benzodiazepine hypnotics such as zopiclone are recommended for treatment of insomnia.[9] However atypical antipsychotics carry a FDA black box warning being associated with increased risk of stroke and death among elderly.

But what does one do when all optimal non pharmacologic and pharmacologic measures fail? That brings us back to the drawing board which in this case led the team to rethink Levetiracetam, a novel new antiepileptic that has been used as monotherapy for partial seizures and adjunctive therapy for generalized tonic clonic and myoclonic seizures. Levetiracetam treated patients have been reported to have psychiatric adverse effects[10] including agitation, hostility, anxiety, apathy, emotional lability, depersonalization, and depressionwith few case reports of frank psychosis [11].While in healthy volunteers levetiracetam is noted to consolidate sleep[12],in patients with complex partial seizures, levetiracetam has been noted to cause drowsiness decreasing day time motor activity and increasing naps without any major effects on total sleep time and sleep efficiency during night.[13]There has been an isolated report of psychic disturbances following administration of levetiracetam and valproate in a patient with epilepsy which resolved following withdrawal of valproate. [14]However in practice it is used for recurrent post TBI seizures as it is a potent AED with a relatively mild adverse effect profile and no clinically significant interactions with commonly prescribed AEDs.[15]

Any adverse drug reaction (ADR) should be evaluated while keeping the patients clinical state in mind. This was, indeed, difficult in our case. With a history of TBI and cognitive decline, it became difficult to ascertain whether the neurocognitive issues were purely due to the nature of TBI or due to an ADR. Assigning causality to a single agent is difficult and fraught with errors. Using the Naranjo algorithm [16], with a score of 7/10(probable ADR) and a notable response on withdrawal of the offending drug as in this case helps establish possible causality.

This is a rare instance where sleep wake cycle disorder and agitation resolved following withdrawal of Levetiracetam in an elderly patient with TBI. This in turn led to the patient having a stable mood so that therapists could communicate and interact with him in order to improve basic cognitive functions such as attention, memory, thinking and executive control. This case illustrates the constant need to systematically and frequently reassess patients as they recover from TBI.

†Appendix: Ranchos Los Amigos Levels of cognitive functioning.

I	No response: Total assistance
II	Generalized response: Total assistance
III	Localized response: Total assistance
IV	Confused-agitated: Maximal assistance
V	Confused-inappropriate, non-agitated: Maximal assistance
VI	Confused-appropriate: Moderate assistance
VII	Automatic-appropriate: Minimal assistance for daily living skills
VIII	Purposeful-appropriate: Stand-by assistance
IX	Purposeful-appropriate: Stand-by assistance on request
X	Purposeful-appropriate: Modified independent

††Naranjo Adverse Drug Reaction Probability Score:

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	

Score

<0 =Doubtful ADR

1-4=Possible ADR

5-8=Probable ADR

>9=Definite ADR

Competing Interests
None declared

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